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Review Article

An Insight on a Neurodegenerative Disease

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Abstract

Multiple sclerosis (MS) is the prototypical inflammatory demyelinating disorder of the central nervous system (CNS) [23]. Although many advances have been made in the comprehension of its pathogenesis, the etiology is still unknown. Several prognostic factors have been suggested in large scale studies, but predictions in individual cases are difficult to make. The prognostic biomarkers of cerebrospinal fluid (CSF), such as 14-3-3 tau, and cystatin C, alpha-1 anti-chymotrypsin, cytokines, chemokines are promising sources of the information about MS with a good potential of quantitative measure, sensitivity, and reliability. However, none has shown sufficient reproducibility to be applied in a clinical practice. This review is addressing the above mentioned biomarkers as MS severity predictors at an early stage. Human tear offers high potential as a non-invasive diagnostic fluid (30). Little work has been done on the role of the secretory immune system (tear, saliva, mucus) in this disease. They infect the host through mucosal surfaces, one may hypothesize that antibodies (Ab) to specific viruses or other immunological markers should be present in the secretions of patients with MS. Since the viral agents (DNA,RNA or mobile genetic elements) implicated in neurodegenerative disease, it is believed that human immuno- deficiency virus (HIV) binds with the antibody so that it is crippled. Thus causes decline in number of T lymphocytes. Though presence of mobile genetic elements have already been accepted but we don't know how to stop them from altering the bio-signaling pathways and causing severe incurable diseases [27].

Keywords: Neurodegenerative; Disease; HIV

TNF-related apoptosis-inducing death ligand (TRAIL) [1], a member of the TNF family, has been shown to be involved in apoptosis during many neurodegenerative diseases. As one of the member of a death ligand family, TRAIL was originally thought to target only tumor cells and was not present in CNS. However, recent data showed that TRAIL was unregulated in HIV-1-infected and immune-activated macrophages, a major disease inducing cell during HIV-1-associated dementia (HAD) [24]. In this review, we summarize the possible common aspects that TRAIL involved those neurodegenerative diseases, TRAIL induced apoptosis signaling in the CNS cells, and specific role of TRAIL in individual diseases.

Early and continuous neurodegeneration

In most patients, MS starts with a relapsing–remitting course (RRMS), with subacute episodes of neurological symptoms that subside spontaneously to apparently normal baseline function. After 15–25 years, however, the relapses typically shift into progressive neurodegeneration, which is termed secondary progressive MS (SPMS; Figure 1a). 10–15% of patients enter this neurodegenerative phase directly from the onset of clinical disease—a condition known as primary progressive MS (PPMS). The majority of patients with MS present in a relapsing-remitting fashion and their first attack presents as unilateral optic neuritis, a brainstem syndrome or partial myelitis. These presentations are known as clinically isolated syndrome (CIS) [19].

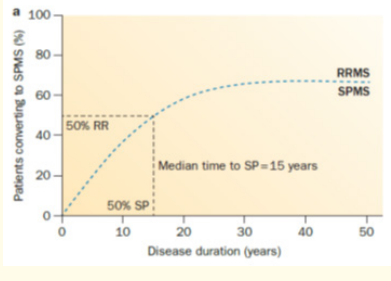

Figure 1a: Clinical correlates of neurodegeneration in MS. 1a | Rate of conversion to SPMS. In a population-based series of 806 patients with RRMS with 28-year follow up, median time to conversion to SPMS (defined as at least 1 year of deterioration) was 15 years, shown here as a cumulative percentage in a Kaplan–Meier analysis. Part a adapted from BMJ Publishing Group Limited [13].

Diagnosis

Diagnostic criteria for MS are mainly based on clinical evaluation, although this is facilitated by supportive laboratory and radiological investigations. In the beginning, the criteria were based on clinical evidence of two relapses that were separated in space (lesions in the different locations in the CNS) and time (at least three months apart) [24]. These criteria were updated in 1983 by the Poser criteria, which allow using also paraclinical evidence such as magnetic resonance imaging (MRI), oligoclonal band (OCB) analysis from cerebrospinal fluid (CSF) and visual evoked potential analysis [22]

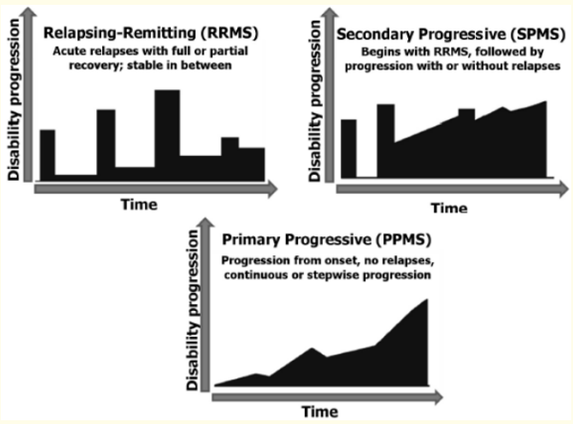

Figure 2: Clinical subtypes of MS. Redrawn from Lublin and Reingold 1996 [15].

Biomarkers in multiple sclerosis

Cytokines: Cytokines are soluble glycoproteins that mediate the pathogenesis of MS. It is generally known that IFN-γ, TNF-α and IL-6 play an important role in MS pathogenesis. Elevated levels of IFN-γ have been detected in the CNS at the peak of EAE disease and treatment of patients with IFN-γ was deleterious to MS patients [21]. Also elevated levels of TNF- α have been detected within MS lesions [11]. TNF- α is also present in higher amount in the serum and CSF of MS patients compared to healthy controls and it also correlates with the severity of the lesions and disease progression [16]. IL-6 has been detected in chronic MS lesions and IL-6 deficient mice were resistant to EAE [21].

Ligand	Receptor	Produced by	Function
TNF-α	TNFR1 TNFR2	Microglia, Astrocytes, T cells	Activates mononuclear cells, induces expression of adhesion molecules and Expressed in the active MS lesions and increased levels are associated with active disease
IFN-γ	IFNGR1 INFGR2	NK, CD8+, Th1 CD4+	Activates mononuclear cells, induces MHC I and MHC II expression, influences antibody production and apoptosis of T cells detect in MS lesions.
TRAIL	TRAIL1, TRAIL2	NK, NKT	Inhibits T-cell activation and mediate apoptosis of neurons and oligodendrocytes.

Table 1

Chemokines: Chemokines are small soluble (8-14 kDa) proteins that are classified into four main families based on the location of intramolecular disulphide bonds (CC, CXC, CX3C, CX) in the N-terminus. In the MS pathogenesis several chemokines and chemokines receptors have been shown to be important. For example, CCL2, CCL4, CCL5, CXCL10, CXCL12, and CXCL13 and their receptors including CCR1, CCR2, CCR5, CXCR3, and CXCR4 have been detected in the active MS lesions, as well as in CSF and blood where they were considered to reflect disease activity [29].

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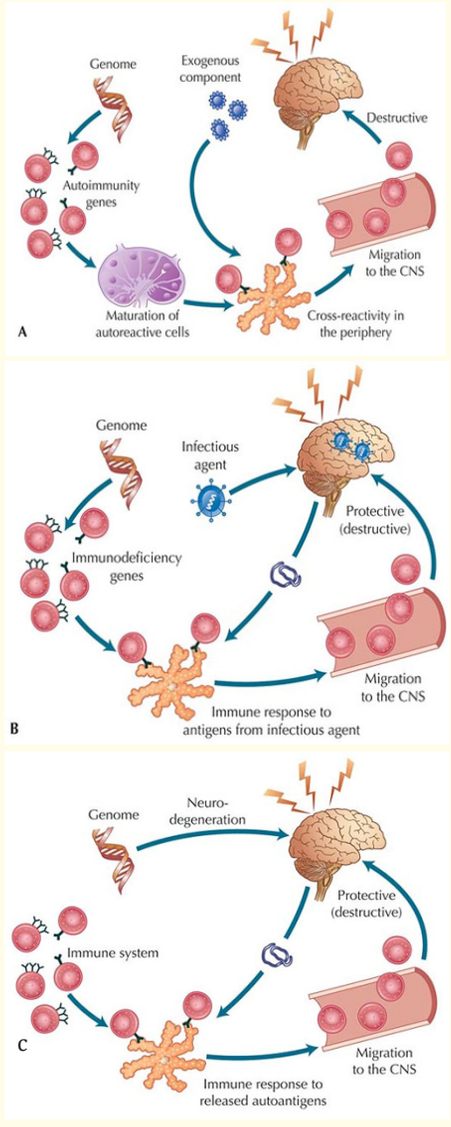

Figure 3: The role of the immune system in multiple sclerosis. The role of the immune systemin a possible autoimmune (panel A), and infectious (panel B), scenario. (CNS—central nervous system.). The role of the immune system in a primary neurodegenerative scenario. (CNS—central nervous system) (Panel c).

Chemokines	Receptors	Target cells	Role in MS
CCL2	CCR2	Monocytes, T cells, NK	Detected in the MS lesions by astrocytes and macrophages
CCL3	CCR1, CCR5	Monocytes	Increased expression of CCL3 in the CSF during active disease

Table 2

TRAIL and general apoptotic signaling leads to cell death

TRAIL (Apo2L, TNFRSF10) is abundantly expressed in immune cells, especially in the NK cells, NKT cells and macrophages [7]. TRAIL receptor mediated signaling events leading to apoptosis can be divided into two distinct pathways, involving either mitochondria (*intrinsic*) or death receptors (*extrinsic*) [8,9].

In the death receptor (*extrinsic*) pathway [26] it has been suggested that death receptors DR4 (TRAIL-R1) and DR5 (TRAIL-R2) oligomerize upon TRAIL binding, the adapter protein Fas-associated death domain (FADD) is then recruited. The receptor-FADD complex then recruits procaspase-8, which forms the death-inducing signaling complex (DISC) where pro-caspase-8 is activated. Depending on the cell type, active caspase-8 can directly lead to the activation of downstream effector caspases, including pro-caspase-3, 6 and 7.

The intrinsic apoptotic pathway [15] is regulated by the balance between pro apoptotic and anti apoptotic members of the B-cell lymphoma 2 (BCL-2) family [5], BCL-2 family protein BID, which interacts with BAX or BAK., activates apoptosome. These activates caspase-9 causing apoptosis as Lesion in MS [12,32]. During this process, Bcl-2 and Bcl-xL appear to directly or indirectly preserve the integrity of the mitochondrial membrane, preventing cytochrome C release and mitochondria mediated cell death initiation. The pro-apoptotic proteins Bax and Bak promote cytochrome C release from mitochondria. Studies using Bax-deficient human colon cancer cells have provided direct evidence that Bax plays a key role in mediating apoptosis induced by certain anti-cancer agents [18].

A schematic diagram illustrating the TRAIL and apoptosis signaling. TRAIL, upon binding to its cognitive receptors, can recruit FADD and pro-caspase-8 to form DISC. DISC releases active caspase-8, two major pathways defined as mitochondria dependent (*intrinsic*) and mitochondria independent (*extrinsic*) pathway. Both pathways finally lead to the activation of effector caspases such as caspase-3, 6, or 7, cause chromatin condensation and the cell apoptosis.

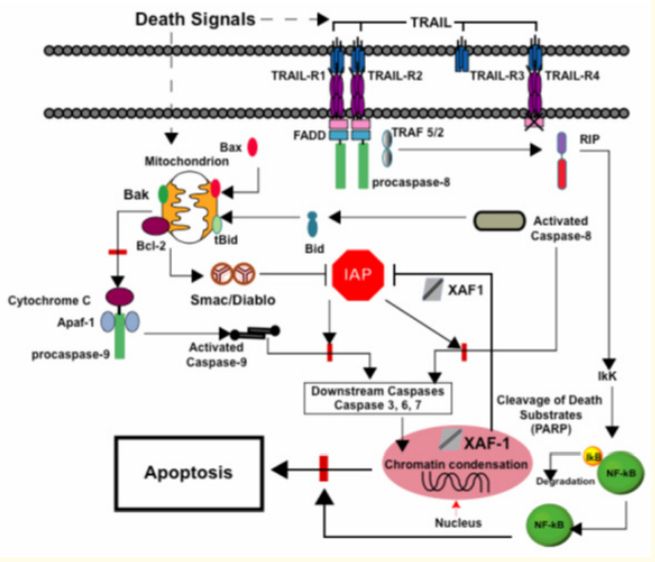

Figure 4

TRAIL in neurodegenerative diseases

TRAIL is not normally expressed in CNS, it is possible that in the neurodegenerative diseases TRAIL expressed on the macrophages which may infiltrate into the brain. Those macrophages may interact with different cell types in the CNS that possess TRAIL receptors causing cell injury or death [15].

TRAIL in HIV-1-associated dementia (HAD)

HAD manifests during the later stages of viral disease as a spectrum of neurological and psychiatric symptoms (17). Cognitive impairments predominate beginning with forgetfulness, loss of concentration, apathy, and may progress to include hallucinations, global cognitive dysfunction and coma. Highly active antiretroviral therapies (HAART) dramatically improved the survival of people living with AIDS and at least temporarily decreased the incidence of HAD. Once affecting 20-50% of adults and children respectively, now less than 10% of all HIV infected subjects develop neurological impairments [25]. Despite this decreased incidence, neurological. TRAIL is up-regulated on macrophages in response to lipopolysaccharide (LPS) [10]. and IFN-α or γ [8]. HIV infection also induces TRAIL [31]. The regulation of TRAIL by these factors, along with its ability to induce neuronal apoptosis, suggests that TRAIL may be involved in the pathogenesis of HAD [24]. TRAIL expressing HIV-1- infected macrophages could initiate neuronal injury.

Mobile genetic elements (DNA and RNA)

Retrovirus containing RNA genome and hexagonal head. Similarly bacteriophage ϕX174 contains single stranded covalently closed circle. Both retrovirus and ϕX174 need a living cell to multiply. Obviously their biochemical supplies come from their host cell. They have temperate and semi-temperate state. How do they differ from a lysogenic λ-bacteriophase? λ continues in two different states, either lytic or lysogenic. How about retrovirus? We think that retrovirus has similarly two states of existence. If we find a way, to induce retroviruses irreversibly then we have solve not only the disease HIV and other incurable neurological diseases even cancer. In basic science, many of us have spent years to learn bacteriophage Mu [32] with a conclusion that mobile DNA elements prevailed.

Conclusion

MS disease activity was associated with up regulation of serum MIF and, TRAIL, and disease progression was associated with increased TRAIL mRNA, MIF and sFas. These observations suggest that these molecules may be candidate biomarkers for disease activity and progression. Altered expression of immune profiles in MS subtypes was found in both protein and gene expression levels. In PPMS, elevated sFas, TNF-α and CCL2 concentrations is consistent with the presence of inflammatory activity in this subtype. gene expression profiles involving genes of Bcl-2 and NF-κB families and death receptor pathway were identified. Up regulation of these pro- and anti-apoptosis molecules indicate the regulatory effect of the immune system in maintaining peripheral homeostasis and thereby preventing pathogenetic events. The increase in sTRAIL was significantly smaller in the MS patients compared with the controls. Hence, activation of MS after delivery may be related to inadequate inhibition of T-cell reactivation after pregnancy in MS.

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